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临床研究

利用数据库分析胃食管反流病的发病因素与临床特点

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摘要:目的 利用完整的前瞻性功能性胃肠病数据库探讨非糜烂性胃食管反流病(NERD)的相关发病因素与临床特点。**方法** 按照病例报告表(CRF)收集完整的个人信息和临床资料,将各项信息与资料录入到网络在线功能性胃肠病数据管理系统,部分病例完成高分辨率食管测压和多通道腔内阻抗-pH监测,导出检索数据进行统计分析。**结果** 在数据库中录入了504例NERD临床资料及152例对照组资料,NERD患者中,女性266例(52.8%)、男性238例(47.2%);商人(23.1%)、公务员(19.6%)、无业(19.2%)、工人(17.1%),城市病源(67.3%)、农村病源(32.7%);平均病程(27.88±16.33)月;不良生活事件(P=0.045,OR=1.954)、长期频繁饮酒(P=0.040,OR=3.957)、打鼾(P=0.002,OR=2.334)、进食夜宵(P=0.002,OR=2.752)、合并焦虑抑郁(P=0.003,OR=2.723)等是NERD的独立危险因素;60.81%NERD患者存在不同程度的食管体部无效收缩,其中存在食管裂孔疝(HH)与无HH的NERD患者两组之间在总液体反流事件方面存在明显差异(P<0.05)。**结论** 不良生活与饮食习惯、焦虑抑郁与不良事件、打鼾、食管运动功能差、HH等与NERD的发病具有重要相关性,30~50岁为高发人群,并与职业和生活区域有一定相关。

关键词:胃食管反流病;数据库;发病因素;病情特点

Risk factors and clinical characteristics of gastroesophageal reflux disease: analysis based on a prospective database of functional gastrointestinal disease

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Abstract: Objective To explore the risk factors and clinical characteristics of non-erosive reflux disease (NERD) based on a prospective single disease database of functional gastrointestinal disease. **Methods** Using a customized case report form, we collected the personal and clinical data of all study participants in an online database for further analysis. High-resolution manometry and multichannel intraluminal impedance-pH monitoring were performed in some cases. **Results** A total of 504 NERD cases and 152 control cases were included in our database. The NERD patients consisted of 266 (52.8%) female patients and 238 (47.2%) male patients; 32.7% of the patients were from rural areas and 67.3% from urban areas; 23.1% of the patients worked in the line of business, 19.6% were civil servants, 19.2% were unemployed, and 17.1% were workers; the mean disease duration of the patients was 27.88±16.33 month. Our analysis showed that adverse events in life (P=0.045, OR=1.954), frequent drinking (P=0.040, OR=3.957), snoring (P=0.002, OR=2.334), late meals (P=0.002, OR=2.752), and anxiety or depression (P=0.003, OR=2.723) were all independent risk factors for NERD. Of these patients, 60.81% had varying degrees of ineffective contraction of the esophageal body. The total liquid reflux events differed significantly between NERD patients with hiatal hernia and those without (P<0.05). **Conclusion** Unhealthy eating habits and lifestyle, history of adverse events, anxiety and depression, snoring, poor esophageal motor function and hiatal hernia are significant factors contributing to NERD, which is related with occupation and living areas and occurs most commonly at 30-50 years of age.

Key words: gastroesophageal reflux disease; single disease database; onset factors; clinical characteristics

胃食管反流病(gastroesophageal reflux disease, GERD)指胃和(或)十二指肠内容物反流入食管引起不适症状和(或)并发症的一种疾病[1],非糜烂性胃食管反流病(NERD)和糜烂性食管炎(EE)为最常见的亚型。GERD患者的生活、饮食习惯的调整与临床特征的评估在GERD的综合治疗上显得尤为重要[2],但目前国内还没有大样本临床数据库探讨NERD患者的发病相关因素与临床特点的报道,我们前期建立了规范化的前瞻性功能性胃肠病临床研究数据库[3],利用该数据库收集了NERD病例,对NERD进行了发病因素与临床特点的深入研究与分析。

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1 资料和方法

1.1 研究对象

1.1.1 纳入病例 所有病例均由消化科专家按照NERD诊断指南[1]确诊,并有内镜检查报告,部分患者依本人意愿完成高分辨率食管测压(HRM)及多通道腔内阻抗-pH监测(MII-pH)。所有患者均按照CRF[3]收集完整

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的个人信息和临床资料,将所有信息与资料录入到网络在线功能性胃肠病数据管理系统并自动检索[3]。

1.1.2 纳入对照组 系患者陪同人员(经问诊无消化系统不适症状)或健康体检者。将在性别、年龄、体质量指数、不良生活饮食习惯、心理状态等各因素方面,与病例组进行比较分析。

1.1.3 排除标准 孕妇或患者正处于哺乳期;就诊或随访期间患者出现严重心肺疾病、消化道恶性肿瘤等全身性疾病;失访病例。

1.2 精神心理状态评定量表

精神心理状态评定量表:所以纳入的病例对照均由本人完善Zung氏焦虑自评量表和Zung氏抑郁自评量表。

1.3 统计方法

采用SPSS 19.0统计软件分析,计量资料以均数±标准差表示,采用两独立样本t检验,计数资料采用χ^2检验或Fisher exact test,危险因素分析采用多因素Logistic回归分析,回归方程中因变量为NERD。本研究以$P<0.05$为差异有统计学意义。

2 结果

2.1 利用数据库对NERD组及对照组一般信息的统计

自2013年9月~2015年9月初步纳入NERD患者512例,3例患者信息不完全,5例患者在随访中发现小肠或出现心肺疾病,目前共504例纳入在线数据库(http://www.fgiddata.com),对照组152例。病例组与对照组的年龄、性别比较,差异无统计学意义。利用数据库的检索统计功能对NERD病例组的一般信息进行统计结果显示:女性266例(52.8%)、男性238例(47.2%),年龄范围在19~76岁,年龄:(42.66±11.90)岁,其中20岁~(16.5%)、30岁~(57.3%)、50岁~(26.2%),高发年龄主要在30~50岁。主要职业分布:商人(23.1%)、公务员(19.6%)、无业(19.2%)、工人(17.1%),城市病源(67.3%)、农村病源(32.7%),体质量指数(BMI)为(22.30±3.30) kg/m^2。主要症状为反流(66.5%)、烧心(58.1%)、嗳气(41.5%)、胸骨后不适(37.3%),其中夜间反流(51.6%)、夜间烧心(56.2%),非典型症状以嗳气、胸骨后不适(胸闷或胸痛)、上腹不适(包括上腹胀及上腹痛)最为常见,食管外症状以咽部异物感或咽部堵塞感常见(表1)。病程(27.88±16.33)月;合并焦虑抑郁216例(42.9%);合并功能性胃肠疾病245例(48.6%);食管裂孔疝67例(13.3%)。组合检索发现95%的无业病例以女性为主;压力大的公务员及商人187例(37.1%);压力大合并不良生活事件346例(68.7%);BMI≥23 kg/m^{2}伴有打鼾的患者192例(38.1%);其余与对照组的一般信息详见表2。

表1 NERD患者症状发生率

Tab.1 Incidence of symptoms of the NERD patients

Symptoms	Number	Ratio (%)
Regurgitation	335	66.5
Night-time reflux	260	51.6
Heartburn	293	58.1
Night-time heartburn	283	56.2
Belching	209	41.5
Retrosternal discomfort	188	37.3
Pharyngeal trouble	248	49.2
Epigastric pain or bloating	143	28.4
Dysphagia	14	2.8
Nausea	45	8.9
Inappetence	19	3.8
Vomiting	4	0.8
Cough	48	9.5
Hoarseness	14	2.8
Asthma	4	0.8

Pharyngeal trouble includes globus sensation and burning tongue; retrosternal discomfort includes retrosternal pain and retrosternal tightness.

2.2 临床特点方面进一步统计分析结果

2.2.1 NERD组与对照组的Logistic回归分析 将两组患者性别、年龄、BMI、生活工作压力、不良生活事件、吸烟史、饮酒、饮茶、静坐时间、睡眠时间、打鼾、日常运动频率、进食夜宵、心理状态等采用二分类Logistic回归分析发现不良生活事件、长期频繁饮酒(饮酒史1年以上且每周3次以上,每次折合酒精大于30 mg)、打鼾、进食夜宵、合并焦虑抑郁等是NERD的危险因素(表3)。

2.2.2 高分辨率食管测压及阻抗-pH监测结果 273例完成高分辨率食管测压的NERD患者60.81%存在不同程度的食管体部无效收缩。在停用质子泵抑制剂状态下进行阻抗-pH监测的231例NERD患者45.45%(105例)表现为总液体反流次数正常但症状相关概率(SAP)阳性,而有HH的NERD组(42例)仅28.57%(12例)(45.45% *vs* 28.57%,P=0.042),NERD并HH组总液体反流事件次数异常所占比例及近端反流占总反流的比均较NERD组患者多(57.14% *vs* 30.30%,P=0.001;86.77±7.15 *vs* 73.63±17.02,P=0.003),存在食管体部无效收缩的患者所占比例也较NERD组患者多(95.24% *vs* 54.55%,P=0.000),但两组DeMeester评分异常患者所占比例无明显差异(P=0.087,表4)。

3 讨论

GERD是多因素造成的消化道动力障碍性疾病,主要发病机制与食管抗反流防御屏障减弱、反流物对食管

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表2 NERD组与对照组的一般特征

Tab.2 General characteristics of NERD group and control group

Characteristics	NERD group	Control group
Gender		
Female	266 (52.8%)	74 (48.7%)
Male	238 (47.2%)	78 (51.3%)
Age (year)		
20~29	83 (16.5%)	37 (24.3%)
30~49	289 (57.3%)	72 (47.4%)
50~	132 (26.2%)	43 (28.3%)
Occupation		
Worker	86 (17.1%)	27 (17.8%)
Farmer	64 (12.7%)	16 (10.5%)
Civil Servant	99 (19.6%)	20 (13.2%)
Intellectual	42 (8.3%)	51 (33.6%)
Merchant	116 (23.1%)	26 (17.1%)
Unemployed	97 (19.2%)	12 (7.9%)
Work and Life stress		
No stress	78 (15.5%)	33 (21.7%)
Common stress	215 (42.7%)	78 (51.3%)
Great stress	171 (33.9%)	36 (23.7%)
Much great stress	40 (7.9%)	5 (3.3%)
History of adverse events		
No	324 (64.3%)	127 (83.6%)
Yes	180 (35.7%)	25 (16.4%)
Having late meals		
No	295 (58.5%)	120 (78.9%)
Yes	209 (41.5%)	32 (21.1%)
Smoking history		
No	399 (79.2%)	113 (74.3%)
Little	38 (7.5%)	23 (15.1%)
Heavy	67 (13.3%)	16 (10.5%)
Drinking history		
No	308 (61.1%)	106 (69.7%)
Occasionally	104 (20.6%)	37 (24.3%)
Frequently	92 (18.3%)	9 (5.9%)
Tea drinking		
No	291 (57.7%)	97 (63.8%)
Yes	213 (42.3%)	55 (36.2%)
Exercise frequency		
More than weekly	114 (22.6%)	82 (53.9%)
Less than weekly	390 (77.4%)	70 (46.1%)
Daily sitting time (h)		
More than 4 h	244 (48.4%)	78 (51.3%)
Less than 4 h	260 (51.6%)	74 (48.7%)
Daily sleeping time (h)		
More than 6 h	157 (31.2%)	130 (85.5%)
Less than 6 h	347 (68.8%)	22 (14.5%)
BMI (kg/m^2)		
≤18.5	52 (10.3%)	10 (6.6%)
18.5~23	216 (42.9%)	96 (63.2%)
23.1~	236 (46.8%)	46 (30.3%)
Waist (cm)		
≤85	281 (65.8%)	104 (68.4%)
85~	175 (34.7%)	41 (27.0%)
≥95	48 (9.5%)	7 (4.6%)
Snore		
No	283 (56.2%)	121 (79.6%)
Yes	221 (43.8%)	31 (20.4%)
Anxiety or depression		
No	288 (57.1%)	138 (90.8%)
Yes	216 (42.9%)	14 (9.2%)

的攻击作用有关[2]，其诱因可能与人们的生活方式改变有关[4]。但具体机制和诱因的分类尚无定论，而且NERD治疗效果欠佳[5]，因此对NERD进行包括流行病学及临床特点、治疗方案、治疗效果等方面的研究具有重要意义。

我们利用数据库中的统计功能发现NERD患者主要症状和高发年龄方面，与以往研究无明显差异，但公务员和商人、无业妇女为高发人群，尤其是城市生活人员更为明显，可能与该人群处于承受事业、家庭压力最多的阶段，生活饮食不规律有关，既往无类似报道。在发病的因素方面发现，不良生活事件、长期频繁饮酒、打鼾、进食夜宵、合并焦虑抑郁等是NERD的独立危险因素，而且可能相互影响，促进病情发展。发病机制方面包括食管体部无效收缩，有HH的NERD患者存在明显的食管动力差、总液体反流事件增多。如Yang等[6]研究发现NERD患者焦虑抑郁评分较正常对照高。而You [7]和Lin 等[8]研究发现GERD患者发生精神疾病的风险较大，可能二者互相影响。Kamolz 等[9]认为精神心理因素可通过影响食管动力及食管下括约肌(LES)的功能而促进胃食管反流(GER)症状的发生。Prakash[10]认为焦虑抑郁可增加食管黏膜的敏感性，因而轻度的食管内刺激便可诱发GER症状[11]。急性心理应激影响GER症状的发生可能是通过促肾上腺皮质激素介导的下丘脑-垂体-肾上腺轴的激活而起作用[12]。睡前进食可使NERD的发生风险增加2.752倍，可能与睡前饮食可引起胃内pH降低有关[13]，导致夜间反流、烧心症状的发生。饮酒可促进胃泌素分泌导致LES压力下降、延迟胃排空[13]，因而长期大量饮酒有可能促进反流的发生。本研究结果显示NERD与打鼾明显相关，有研究显示原发性鼾症患者GERD的发病率高且大多伴有BMI明显增高[14]，并较其它耳鼻喉科疾病患者更易出现咽喉反流症状[15]。打鼾伴睡眠呼吸暂停综合征(OSAHS)的患者存在食管上、下括约肌结构和功能障碍[16]。Ing 等[17]认为打鼾伴OSAHS的患者在呼吸暂停的过程中因胸内负压和食管内负压增高导致LES跨膈压差增大，当超过LES张力时，则可因“吸吮”作用促进反流可能起夜间明显症状。无HH与有HH的患者相比，前者反流(-)SAP(+)的患者所占比例较大，提示内脏高敏感在单纯NERD的发病中发挥着重要的作用，而后者总液体反流次数异常所占比例、近端反流占比较前者高，表明合并HH的患者不仅食管的结构存在异常且动力也明显下降，导致抗反流屏障功能受损而反流事件增多。总之，NERD具有自身特有的发病因素与临床特色，为指导NERD临床治疗研究和帮助患者避免有害因素、减少反流、改善症状，提供了有力的依据。

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表3 NERD组与对照组的二分类logistic回归分析

Tab.3 Logistic regression analysis of the risk factors of NERD

Factor	Std.Error	*P*	*β*	OR	95%CI
History of adverse events	0.333	0.045	0.670	1.954	[1.017, 3.756]
Late meals	0.327	0.002	1.012	2.752	[1.449, 5.228]
Snore	0.275	0.002	0.848	2.334	[1.361, 4.004]
Frequent drinking	0.669	0.040	1.375	3.957	[1.067, 14.673]
Anxiety or depression	0.337	0.003	1.002	2.723	[1.407, 5.267]

表4 有或无食管裂孔疝的NERD患者高分辨率食管测压及多通道腔内阻抗-pH监测结果比较

Tab.4 Comparison of HRM and MII-pH between NERD patients with hiatal hernia and those without

Item	NERD	NERD with hiatal hernia	χ^2/t	*P*
Abnormal DeMeester score	40	12	χ^2=2.920	0.087
Abnormal total reflux events	70	24	χ^2=11.340	0.001
Abnormal weakly acidic reflux events	133	18	χ^2=3.115	0.078
Abnormal weakly alkaline reflux events	53	1	χ^2=9.470	0.002
SAP positive for weakly acidic reflux	80	12	χ^2=0.584	0.445
SAP positive for acid reflux	67	12	χ^2=0.003	0.955
Normal total reflux events with SAP positive	105	12	χ^2=4.136	0.042
Ineffective body esophageal motility	126	40	χ^2=24.692	0.000
Ratio of proximal reflux	73.63±17.02	86.77±7.15	t=-3.274	0.003

Normal values is according to the value of corresponding instrument.

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